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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/573,764	XIA ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	IAN DANG	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 15 December 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1,3-5,7-9,15-21,31,32,36-38,43,45 and 47-54 is/are pending in the application.
- 4a) Of the above claim(s) 3-5,7-9,16-21,31,32,36-38,43,45 and 47-50 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,7-9,15 and 51-54 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 18 June 2008 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>06/25/2008</u> .  | 6) <input type="checkbox"/> Other: _____                          |

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## **DETAILED ACTION**

### ***Election/Restrictions***

Applicant's election of Group I, claims 1, 7-9, 15, and 45, in the reply filed on 12/15/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

### ***Status of Application, Amendments and/or Claims***

The amendment of 15 December 2008 has been entered in full. Claims 2, 6, 10-14, 22-30, 33-35, 39-42, 44, and 46 have been cancelled and claims 1 and 15 have been amended. Claims 51-54 have been added. Claims 3-5, 16-21, 31, 32, 36-38, 43, 47-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 7-9, 15, 45, and 51-54 are under examination.

### **Information disclosure statement**

The information disclosure statement filed 10/31/2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

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The reference by Dublin et al. has not been considered because it does not have any number associated with the patent. In addition, the reference Gen Bank Accession number AF211189 has not been considered by the Examiner because it does not have a publication date and does not have any references associated with the manuscript. Please submit a courtesy copy of the references and a new PTO-1449.

### ***Drawings***

The drawings for Figures 5 and 6 are objected to because it is not clear which SEQ ID NOs correspond to the nucleic acid sequence for  $\alpha_{1I-1}$  or  $\alpha_{1I-2}$ . For instance, for Figure 6 the description of the drawing indicates the alignment for the nucleic acid sequences of SEQ ID NO:19 and SEQ ID NO:21 (page 29), but Figure 5 does not refer to those sequences with any SEQ ID NOs. Instead Figure 6 only refers to each sequence with  $\alpha_{1I-1}$  or  $\alpha_{1I-2}$ . The same objection applies to Figure 5.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant

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will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

In addition, on page 29 of the specification, the description of the drawings for Figures such as 1 and 4, which have various parts, need to be identified as such in the brief description (ex. "Figures 1A-B...").

### ***Claim Objections***

Claims 1, 8, and 15 are objected to because of the following informalities:

The recitation of "splicing" variant in claims 1, 8, and 15 is indefinite because the accepted term is "splice" variant. The recitation of "splice" variant would overcome the rejection.

### ***Claim Rejections - 35 USC § 101/112***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The examiner is using the following definitions in evaluating the claims for utility.

"Specific" – A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention.

"Substantial" – A utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

"Credible" – Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record that is probative of the Applicant's

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assertions. That is, the assertion is an inherently unbelievable undertaking or involves implausible scientific principles.

See also the MPEP at § 2107-2107.02.

Claims 1, 7-9, 15, 45, and 51-54 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, and credible utility or, in the alternative asserted utility or a well established utility.

The claims are drawn to an isolated nucleic acid molecule of an alternative splicing variant of a human T-type calcium channel subunit, comprising a sequence of nucleotides encoding a T-type calcium channel  $\alpha_{1L-1}$  subunit.

The specification discloses the following facts regarding the claimed isolated nucleic acid molecule of an alternative splicing variant of a human T-type calcium channel subunits  $\alpha_{1L-1}$  and  $\alpha_{1L-2}$ :

- At page 10, the specification teaches that the isolated nucleic acid molecule of an alternative splicing variant of a human T-type calcium channel subunit encodes a spliced T-type calcium channel subunit of human T-type calcium channel (lines 1-4).
- The nucleotide encoding a T-type channel  $\alpha_{1L-1}$  subunit is a single nucleotide polymorphism of the reference sequence that has the GeneBank# AF211189 (page 10, lines 10-12) and the nucleotide encoding a T-type channel  $\alpha_{1L-2}$  subunit is splice variant of the reference sequence GeneBank# AF211189 (page 10, lines 12-13).
- The novel variant encoding sequence(s) of the invention are not merely truncated forms or fragments of the known gene, but rather novel sequences, which naturally

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- occur within the body of individuals and may thus have physiological relevance. The inventors have discovered that one of the herein disclosed nucleotide sequences encoding one of the  $\alpha_{11}$  calcium channel subunit isoforms (variant #1, SEQ ID NO: 19 differs from the reference sequence in at least one (1) amino acid, .e.g., at position 1005, specifically Isoleucine (I) at position 1005 of the reference sequence is valine in the novel isoform of the invention - vis-à-vis I 1005 > V 1005. The other variant (isoform - #2) contains a 54 nucleotide insert (SEQ ID NO:20) encoding eighteen (18) amino acid residues relative to SEQ ID NOS: 18 and 19 after amino acid 679 of SEQ ID NO:19 (page 10, lines 15-24).
- At pages 86-95, the specification provides examples for isolation of the calcium channel  $\alpha_{11}$  (Example 1 page 86), the generation of a stable cell line for the human calcium channel channel  $\alpha_{11-1}$  subunit (Example 2 page 90), the production of antisera and immunoblot analyses using an antibody binding to the  $\alpha_{11-1}$  subunit (Example 3, page 91; Figure 1) and the functional expression of the human calcium channel  $\alpha_{11-1}$  subunit (example 4, page 92; Figures 2-4).

However, the instant specification does not teach any specific functional characteristics of the claimed isolated nucleic acid molecule of an alternative splicing variant of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$ . Although the specification discloses that the nucleic acid molecule of an alternative splicing variant of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$  may have the same physiological activity as the reference  $\alpha_{11}$  (page 39, lines 1-3), the specification does not provide any information regarding the isolated nucleic acid molecules of an alternative splicing variant of a human T-type calcium channel subunits  $\alpha_{11-1}$  or  $\alpha_{11-2}$  in the context of a cell or organism or any methods or working examples that indicate that the nucleic

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acid molecules of the instant invention is involved in any activities or diseases states. The isolation and calcium assays of the alternative splicing variant of a human T-type calcium channel subunits  $\alpha_{1L-1}$  and  $\alpha_{1L-2}$  do not provide sufficient evidence regarding the specific functional characteristics of the alternative splicing variant of a human T-type calcium channel subunits  $\alpha_{1L-1}$  and  $\alpha_{1L-2}$ . Since significant further research would be required of the skilled artisan to determine how the alternative splicing variant of a human T-type calcium channel subunits  $\alpha_{1L-1}$  and  $\alpha_{1L-2}$  are involved in any activities, the asserted utilities are not substantial. Since the utility is not presented in mature form and significant further research is required, the utility is not substantial. The specification asserts the following as patentable utilities for the claimed nucleic acid molecules of an alternative splicing variant of a human T-type calcium channel subunits  $\alpha_{1L-1}$  and  $\alpha_{1L-2}$  :

- 1) to screen test compounds for modulating channel activity (page 17, lines 9-27)
- 2) to provide antibodies which specifically bind to the proteins may be used for the diagnosis of conditions or diseases characterized by or associated with over- or under-expression of the proteins of the invention (page 20, lines 24-31)
- 3) to provide a method of diagnosis of a disease associated with alternative splicing variant of a human T-type calcium channel subunits  $\alpha_{1L-1}$  and  $\alpha_{1L-2}$  (page 19, line 29 to page 30 line 23)

Each of these shall be addressed in turn.

1) *to screen library of compounds for drug discovery.* This asserted utility is not specific or substantial. Such assays can be performed with any polypeptide or polynucleotide. Nothing is disclosed about how the alternative splicing variant of a human T-type calcium channel subunits  $\alpha_{1L-1}$  and  $\alpha_{1L-2}$  is affected by the compounds. Additionally, the specification discloses

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nothing specific or substantial for the compounds that can be identified/selected/validated by this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

*2) to provide a method of generating antibodies which specifically bind to at least a portion of a calcium channel protein.* This asserted utility is not specific or substantial. Such method can be performed with any polypeptide. Although the specification discloses that the antibody binds to human calcium channels (page 20, lines 34-35), the specification also discloses nothing about antibodies binding the alternative splicing variant of a human T-type calcium channel subunits  $\alpha_{1L-1}$  and  $\alpha_{1L-2}$  or how antibodies can be used to diagnose a condition associated with the alternative splicing variant of a human T-type calcium channel subunits  $\alpha_{1L-1}$  and  $\alpha_{1L-2}$ . In addition, the specification does not disclose any disorders associated with the alternative splicing variant of a human T-type calcium channel subunits  $\alpha_{1L-1}$  and  $\alpha_{1L-2}$ . Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

*3) to provide a method for a compound useful for a treatment a disease associated with the alternative splicing variant of a human T-type calcium channel subunits  $\alpha_{1L-1}$  and  $\alpha_{1L-2}$ .* This asserted utility is not specific or substantial. The disclosed method of can be performed with any or polynucleotides or polypeptides. Further, the specification does not disclose a specific disease or condition associated with nucleic acid molecules of the alternative splicing variant of a human T-type calcium channel subunits  $\alpha_{1L-1}$  and  $\alpha_{1L-2}$ . Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

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The presence of the calcium influx cannot be reliably used to predict the function of the nucleic acid molecules of the alternative splicing variants of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$ . For instance, the examples of Figures 2-4 disclosing the calcium influxes in wild type cells, B21 cells, and T-Rex cells, do not provide any support for any specific functions. From the specification these teachings in the specification are mere suggestions for experimental investigation to determine what activities the nucleic acid molecules of the alternative splicing variants of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$  might have and what practical use may be derived from such activities.

Therefore, the information regarding the nucleic acid molecules of the alternative splicing variants of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$  in the specification does not establish the claimed protein has a credible, specific, and substantial utility

Claims 1, 7-9, 15, 45, and 51-54 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, credible utility, asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

***Claim Rejections - 35 USC § 112, First paragraph (Written Description)***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 1, 7-9, 15, 45, and 51-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 7-9, 15, 45, and 51-54 are drawn to biologically active fragments of the polynucleotide of the alternative splicing variants of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$  of SEQ ID NO:18 and SEQ ID NO:20.

Although Applicant discloses the full length polynucleotides of SEQ ID NO:18 and SEQ ID NO:20 for the nucleic acid molecules of the alternative splice variants of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$ , Applicant has not provided any information regarding the identifying structural characteristics of functional fragment or nucleic acid residues of the polynucleotide sequences of SEQ ID NO:18 and SEQ ID NO:20 that are required for biological activity. The specification and the claim fail to disclose any structural identifying characteristics of the fragments or the nucleic acid molecules of the polynucleotide for the alternative splice variants of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$ .

Therefore, Applicant has not satisfied the requirement for written description because the claimed functional fragments or nucleic acid residues for the polynucleotide sequences of SEQ ID NO:18 and SEQ ID NO:20 of claims 1 and 15 encompass a genus of nucleic acid molecules of the alternative splicing variants of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$ , which include variants, mutants, and derivatives whose identifying characteristics required for biological activity are not described. The specification provides the polynucleotide sequences of SEQ ID NO:18 and SEQ ID NO:20, but it does not provide any description of the

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special features for the claimed functional fragments or nucleic acid residues of the polynucleotide sequences of SEQ ID NO:18 and SEQ ID NO:20 that are required for biological activity. Furthermore, the specification does not provide any teachings sufficient to one of skill in the art to identify the numerous functional fragments or nucleic acid residues for the polynucleotide sequences of SEQ ID NO:18 and SEQ ID NO:20 encompassed by the claims. Thus, Applicants have not provided any identifying structural characteristics or properties of the instant functional fragments or nucleic acid residues of the polynucleotide sequences of SEQ ID NO:18 and SEQ ID NO:20, such that one of skill would be able to predictably identify the encompassed the fragments or nucleic acid residues of the polynucleotide sequences of SEQ ID NO:18 and SEQ ID NO:20 required for biological activity for the calcium channel in the instant claims.

Based on Applicants' disclosure and knowledge within the art, those of skill in the art would conclude that Applicants would not have been in possession of the claimed genus of functional fragments or nucleic acid residues for the polynucleotide sequences of SEQ ID NO:18 and SEQ ID NO:20 required for biological activity based on the disclosure of the full length polynucleotide of SEQ ID NO:18 and SEQ ID NO:20. Thus, applicant was not in possession of the claimed genus and the written description requirement is not satisfied.

***Claim Rejections - 35 USC § 112 (Enablement)***

Furthermore, even if claims 1, 7-9, 15, 45, and 51-54 possessed utility under 35 USC 101, they would still be rejected under 35 USC 112, first paragraph, because the specification, while being enabling for the full length polynucleotides of the alternative splicing variants of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$  of SEQ ID NO:18 and SEQ ID NO:20,

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does not reasonably provide enablement for biologically active fragments or nucleotides degenerate to the genetic code of the polynucleotide of the alternative splicing variants of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$  of SEQ ID NO:18 and SEQ ID NO:20.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Claims 8 and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated recombinant host cell comprising a polynucleotide encoding T-type calcium channel subunits in culture, does not reasonably provide enablement for a recombinant host cell transfected *in vivo* with a polynucleotide encoding T-type calcium channel subunits for the purpose of gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include: (1) Nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the breadth of the claims, (7) the quantity of experimentation needed, (8) relative skill of those in the art.

#### Nature of the invention and breath of the claims

The claimed invention is drawn to functional fragments or biologically active fragments or nucleic acid residues for the polynucleotide sequences for the alternative splicing variants of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$  of SEQ ID NO:18 and SEQ ID NO:20.

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The invention is excessively broad because the recitation of claims 1 and 15 encompass an excessive number of fragments for the polynucleotide sequences for the polynucleotide of the alternative splicing variants of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$ . The recitation of the words "biologically active fragments" and are interpreted to include fragments a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$  that can be as few as 12 nucleic acids. However, the specification does not provide any guidance regarding the fragments or nucleic acid residues of the polynucleotide sequences of SEQ ID NO:18 and SEQ ID NO:20 required for biological activity of the claimed calcium channel. The recitation of claims 1 and claim 15 includes a large number of polynucleotides encoding the human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$ .

Due to the large quantity of experimentation necessary to determine the functional fragments or biologically active fragments or nucleic acid residues for the polynucleotide sequences for the alternative splicing variants of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$ , the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, and the unpredictability of determining the functional fragments or biologically active fragments or nucleic acid residues for the polynucleotide sequences, undue experimentation would be required of the skilled artisan to make the claimed functional fragments or biologically active fragments or nucleic acid residues for the polynucleotide sequences for the alternative splicing variants of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$ .

Finally, claims 8 and 52 are drawn to a recombinant host cell transfected by an expression vector comprising a nucleotide encoding a human T-type calcium channel subunits. The invention is broad because the recitation of claims 8 and 52 encompasses any recombinant

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host in either *the in vitro* or *in vivo* environment. The breath of the claims includes the uses of the claimed invention for gene therapy.

#### Unpredictability and state of the art

The art of gene therapy is not predictable because vectors delivering DNA, such as the claimed invention in this instant application, have not been optimized for use in humans. Verma et al. (1997) teach that the Achilles heel of gene therapy is gene delivery because the problem has been an inability to deliver genes efficiently and to obtain expression (page 239, column 3, 2<sup>nd</sup> paragraph). The first approach comprising the non-viral vectors, ranging for direct injection of DNA to mixing the DNA with polylysine or cationic lipids suffer from poor efficiency of delivery and transient expression of the gene. In another approach the use of viruses is a powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system fighting off the virus and hampering the attempts to deliver genes in viral vectors. In view of these teachings, the use of a nucleotide encoding a human T-type calcium channel subunits in a recombinant host cell *in vivo* is unpredictable. Thus Applicants are not enabled for the claimed invention because they have not provided any support overcoming the unpredictability of using a nucleotide encoding a human T-type calcium channel subunits for gene therapy in the specification.

#### The amount of direction or guidance present

Applicants' disclosure is limited to the characterization of the full length SEQ ID NO:18 and SEQ ID NO: 20. However, the specification does not provide guidance or direction regarding any structural characteristics for the polynucleotides encoding the human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$  that required for biological activity.

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Moreover, the specification does not provide guidance or direction regarding how to administer the claimed polynucleotide encoding the human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$  to cells *in vivo*. The *in vivo* uses of a polynucleotide in gene therapy require methods for using the claimed invention, such as delivery vectors or transfection reagents, that have not been optimized at present time.

#### Working Examples

Although Applicant has disclosed that the full length of SEQ ID NO:18 and SEQ ID NO:20 corresponding to the polynucleotides encoding the human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$  (Figure 6), the specification does not provide any examples for biologically active fragments or nucleic acid residues for the polynucleotides of the alternative splicing variants of the human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$  of SEQ ID NO:18 and SEQ ID NO:20.

In addition, for a polynucleotide encoding a protein the specificity for delivering the construct to a specific cell population depends on the vector delivering the polynucleotide encoding the human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$ . In view of the unpredictability of DNA delivery vectors, the lack of working examples contributes to the unpredictability of the art.

#### The quantity of experimentation needed

It would require undue experimentation for one of skill in the art to be able to use the claimed for the biologically active fragments or nucleic acid residues the polynucleotide of the alternative splice variants of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$  of SEQ ID NO:18 and SEQ ID NO:20 because the specification and claims have not provided the structural

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identifying characteristics of the biologically active fragments and nucleic acid residues of the polynucleotides for the human T-type calcium channel subunit  $\alpha_{1I-1}$  and  $\alpha_{1I-2}$ . Thus one of skill the art would not be able to use the claimed biologically active fragments or nucleic acid residues of the polynucleotide for the alternative splicing variants of the human T-type calcium channel subunits  $\alpha_{1I-1}$  and  $\alpha_{1I-2}$  of SEQ ID NO:18 and SEQ ID NO:20 because the specification has not provided enough information.

Finally, the Examiner has interpreted claims 8 and 52 as reading a recombinant host cell in the context of a multicellular, transgenic organism and host cells intended for gene therapy. Due to the large quantity of experimentation necessary to introduce and express the polynucleotide encoding the human T-type calcium channel subunits  $\alpha_{1I-1}$  and  $\alpha_{1I-2}$  in a cell of an organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce the polynucleotide encoding the human T-type calcium channel subunits  $\alpha_{1I-1}$  and  $\alpha_{1I-2}$  in the cell of an organism to be able produce the human T-type calcium channel subunits  $\alpha_{1I-1}$  and  $\alpha_{1I-2}$  polypeptide, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of gene therapy and the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. (Please note that this issue could be overcome by amending the claims to recite, for example, "An isolated recombinant host cell...").

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***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 7-8, 15, 45, 51-52, and 54 are rejected under 35 U.S.C. 102(a) as being anticipated by Dietrich et al. (US2002/0150911; filed 08/23/2001; published 10/17/2002).

The claimed invention is drawn to biological fragments of nucleic acid molecules for the alternative splicing variants of a human T-type calcium channel subunits  $\alpha_{11-1}$  and  $\alpha_{11-2}$  of SEQ ID NO:18 and SEQ ID NO:20, which encode a polypeptide capable of forming a functional T-type calcium channel. In addition, the claimed invention includes an expression vector comprising the nucleic acid molecule of SEQ ID NO:18 and SEQ ID NO:20 and a recombinant host cell transfected by the expression vector in which the expression vectors encoding the calcium channel subunits are sufficient for assembly of a functional voltage-gated calcium channel. Finally, the invention is drawn to a recombinant cell line comprising a host cell transformed with a polynucleotide expressing a polypeptide isoform of the T-type calcium channel  $\alpha_{11}$ .

Dietrich et al. teach the SEQ ID NO:3 (pages 28-36 of Dietrich et al.) that is a biological fragment of a polynucleotide for a human T-type calcium channel of SEQ ID NO:18 (see Exhibit A) and of SEQ ID NO:20 (see exhibit B).

Although the reference by Dietrich et al. does not teach that the isolated polynucleotide of SEQ ID NO:3 encodes a polypeptide capable of forming a functional T-type calcium channel,

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the polynucleotide of SEQ ID NO:3 would inherently encode a polypeptide capable of forming a functional T-type calcium channel because the name of the polynucleotide "T-type calcium channel subunit variants (TCCV-1 and TCCV-2)" (page 1, paragraph [0008]) provides its functional activity and the use of the polynucleotide encoding the polypeptide TCCV-1 or TCCV-2 in the screening of compound that requires modulation of TCCV-1 or TCCV-2 activity (page 1, paragraph [0013]). From these the disclosures of Dietrich et al., the polynucleotide of SEQ ID NO:3 inherently encodes a polypeptide capable of forming a functional T-type calcium channel.

These teachings by Dietrich et al. meet the limitations of claims 1 and 15.

Furthermore, the reference by Dietrich et al. teaches an expression vector comprising the nucleic acid of SEQ ID NO:3 encoding a human T-type calcium channel subunits  $\alpha_{11}$  (page 1, paragraph [0010]) and a promoter operably associated or operably linked with a coding sequence if the promoter controls the translation or expression of the encoded polypeptide (page 5, paragraph [0050]) meeting the limitations of claims 7 and 51.

In addition, the reference by Dietrich et al. teaches a recombinant host cell transfected by the expression vector comprising the nucleotide of SEQ ID NO:3 encoding the human T-type calcium channel subunit  $\alpha_{11}$  (page 1, paragraph [010]) meeting the limitations of claims 8 and 52.

Finally, the reference by Dietrich et al. teaches that a recombinant cell line comprising a host cell transformed with a polynucleotide expressing a polypeptide isoform of the T-type calcium channel  $\alpha_{11}$  (page 1, paragraph [0010] and page 50, claims 8-11) meeting the limitations of claims 15 and 54.

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***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dietrich et al. (US2002/0150911; filed 08/23/2001; published 10/17/2002) as applied to claims 1, 7-8, 15, 45, 51-52, and 54 in further view of Catterall et al. (2000, Annual Review Cell and developmental biology, Volume 16, page 521-555) .

The teachings of Dietrich et al. are set forth above. However, the reference by Dietrich et al. does not teach that the cell transformed with DNA expression vectors encodes any additional calcium subunits necessary and sufficient for assembly of a functional voltage-gated calcium channel.

Catterall et al. (2000) teach that human T-type voltage-gated calcium channels are made up of different subunits for their functional activities that include  $\alpha 1$  and multiple  $\beta$  subunits (page 529).

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Under *KSR*, it's now apparent "obvious to try" may be an appropriate test in more situations than we previously contemplated. When there is motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try may show that it was obvious under § 103 (*KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, \_\_\_, 82 USPQ2d 1385, 1397 (2007)).

Thus, it would have been obvious for one skilled in the art to modify the transformed cell with the polynucleotide encoding alternative splicing variants of a human T-type calcium channel subunits as taught by Dietrich et al. by adding to the cell transformed any additional DNA expression vectors encoding additional calcium subunits necessary and sufficient for assembly of a functional voltage-gated calcium channel as taught by Catterall et al. One of ordinary skill in the art at the time the invention was made would have been motivated to add to the cell transformed with any DNA expression vectors encoding additional calcium subunits because "a person of ordinary skill has good reason to pursue the know options within is or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." In addition, one skill in the art would have been motivated to add additional DNA expression vectors encoding subunits of the calcium channel in order to have a proper functional voltage-gated calcium channel because it is well know in the art, as exemplified by Caterall et al., that human T-type calcium channels require the association of multiple different subunits for their functional activities. Accordingly, the invention taken as a whole is prima facie obvious.

### Conclusion

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No claim is allowed.

### **Information**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to IAN DANG whose telephone number is (571)272-5014. The examiner can normally be reached on Monday-Friday from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ian Dang  
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Art Unit 1647  
January 29, 2009

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